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Ethical, legal, and social implications (ELSI) and challenges in the design of a randomized controlled trial to test the online return of cancer genetic research results to U.S. Black women

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Abstract

Background—A central challenge to precision medicine research efforts is the return of genetic research results in a manner that is effective, ethical, and efficient. Formal tests of alternate modalities are needed, particularly for racially marginalized populations that have historically been underserved in this context.

Methods—We are conducting a randomized controlled trial (RCT) to test scalable modalities for results return and to examine the clinical utility of returning genetic research results to a research cohort of Black women. The primary aim is to compare the efficacy of two communication modalities for results return: 1) a conventional modality that entails telephone disclosure by a Board-certified genetic counselor, and 2) an online self-guided modality that entails results return directly to participants, with optional genetic counselor follow-up via telephone. The trial is being conducted among participants in the Black Women's Health Study (BWHS), where targeted sequencing of 4,000 participants was previously completed.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Results—Several ethical, legal, and social implications (ELSI) and challenges presented, which necessitated substantial revision of the original study protocol. Challenges included chain of custody, re-testing of research results in a CLIA lab, exclusion of VUS results, and digital literacy. Bioethical principles of autonomy, justice, non-maleficence, and beneficence were considered in the design of the study protocol.

Conclusion—This study is uniquely situated to provide critical evidence on the effectiveness of alternative models for genetic results return and provide further insight into the factors influencing access and uptake of genetic information among U.S. Black women.

Keywords

Return of results; hereditary cancer; genetic counseling; disclosure modality; eHealth; ELSI; Black women

1. Background

A central challenge to large-scale precision medicine research is the return of individual genetic research results to participants [1, 2]. With updates in federal regulations promoting transparency and greater access to clinical and research test results, research paradigms have been proposed for returning individual research results to participants [3]. A conceptual framework proposed in a 2018 report from the National Academics of Sciences, Engineering, and Medicine outlined two dimensions that guide decisions on returning individual research results: 1) the potential value of the result to the participant, and 2) the feasibility of the return [3]. Although studies have reported that research participants are interested in (and even expect) individual genetic research results [4–6], best practices for how to increase the feasibility of these efforts have yet to be elucidated. The scale of these endeavors has renewed concerns about the shortage of genetic counselors and has intensified calls to examine the utility of alternate modalities for communicating genetic results [7, 8] and expand research efforts to provide the much-needed evidence base [3].

Alternate modalities of providing genetic counseling and results disclosure are increasingly being proposed to address the growing demand for services, the shortage of genetic counselors, and the need to expand access to genetic information [7, 9, 10]. Some efforts have focused on the use of telephone counseling or videoconferencing as a means to expand access to genetic services [11–15]. Although these approaches address logistical barriers such as geography and distance from genetic service providers, they do not address the time challenges associated with providing pretest education, ensuring informed consent, and conducting results disclosure [16, 17].

The use of digital solutions has often been proposed as a supplement to counseling to increase efficiency and use of genetic counselors [7, 16–18]. Online modalities that provide direct-access to genetic results have been used in various contexts including research [8, 10, 19, 20] and industry [21], yet few studies have formally tested this approach in terms of its acceptability and effectiveness compared to conventional genetic counseling approaches to results disclosure [7, 10, 22]. An exception is a randomized non-inferiority trial, which compared a web-based platform to in-person genetic counseling for returning carrier results

from exome sequencing [8]. Results from that study demonstrated that the web-based platform was non-inferior to the in-person counselor for knowledge, psychological distress, and decisional conflict at follow-up, suggesting that an online modality may be effective for subsets of test results.

In the context of clinical testing, prior studies have consistently shown that Black women are less likely to pursue *BRCA* testing and learn their genetic risk, even when offered [23–28]. In the context of genomic sequencing research, studies have similarly found that uptake of genomic research results is lower among nonwhite participants [29], raising concerns about disparities in access. There is some evidence that Black individuals may have a stronger preference to not involve health care providers in results disclosure, and prefer to review their results independently [30], suggesting that modalities that facilitate the latter may influence engagement and decisions to learn individual genetic research results. Our own preliminary survey research suggested that women in the Black Women's Health Study (BWHS) cohort prefer self-guided modalities for results disclosure compared to results disclosed by a health care professional such as a genetic counselor.

The effective translation of precision medicine research will require a concerted effort to engage racial/ethnic minoritized participants in research and increase the generalizability of findings to help ensure disparities are not magnified [23, 31–33]. The present study will not only test alternate modalities to facilitate greater access to genetic information, but it will also provide much needed evidence on how alternate modalities for genetics education and results disclosure might influence test result uptake among a racially underrepresented population in the United States.

2. Methods

2.1. Study Objectives

This randomized controlled trial (RCT) was designed to test alternate communication modalities for cancer genetic research results disclosure. The primary aim of this study is to compare the efficacy of two communication modalities for returning hereditary cancer genetic research results to Black women: 1) a conventional modality that entails telephone disclosure by a Board-certified and licensed genetic counselor (control arm), and 2) an online self-guided modality that entails returning results directly to participants via a secure web platform, with optional genetic counselor follow-up via telephone (intervention arm). The primary outcomes of this study focus on psychosocial and decisional outcomes that have been examined in other noninferiority trials testing genetic communication interventions [12, 34]. These include the decision to learn genetic research results (test uptake), decision uncertainty, knowledge acquisition, and psychological reactions to learning genetic results (test-specific distress, anxiety, depression). Secondary aims of this study will examine 1) moderators of the intervention impact and 2) psychosocial, sociodemographic, and clinical predictors of result uptake.

2.2. Study Sample

The Black Women's Health Study (BWHS) is an ongoing prospective cohort study of 59,000 self-identified Black women from across the U.S. who have been successfully followed since 1995 [35]. Germline DNA samples from 4,363 BWHS women (1,454 breast cancer cases, 2,909 unaffected controls) have previously undergone targeted sequencing of *BRCA1/2* and other known or suspected high/moderate penetrance cancer susceptibility genes as part of a large collaborative study of breast cancer predisposition gene to investigate genetic etiology of breast cancer in Black women [36, 37].

2.3. Eligibility Criteria, Recruitment and Enrollment

Figure 1 depicts the study workflow. BWHS participants are eligible for the trial if their samples had been included in the previous sequencing, they are still living and not lost to follow-up, and have no known cognitive impairments (previously reported to BWHS). Notably, women with a prior cancer diagnosis were eligible for the trial due to the utility of genetic information for understanding risks for secondary and other cancers, as well as risks for family members who might benefit from cascade testing. Moreover, participants with only variant(s) of uncertain significance (VUS) identified are not eligible for the trial due to inconsistent classification across Clinical Laboratory Improvement Amendments (CLIA) certified labs and poor characterization among women of African ancestry [38, 39].

Eligible women will be approached by either email or postal mail, depending on prior engagement preferences with BWHS, with a study brochure, recruitment letter, informed consent document, and baseline survey. Both online and paper formats are offered to maximize accessibility to eligible participants and increase the likelihood of enrollment and survey completion.

2.4. Biospecimen Collection, CLIA lab testing and Randomization

Women who enroll in the trial by providing informed consent and completing the baseline survey are sent a DNA collection kit via U.S. Postal Service with detailed instructions to return a saliva sample for confirmation testing in a CLIA-certified laboratory of prior research sequencing results for 18 genes. Once samples are tested, participants are stratified by cancer status (affected/unaffected) and gene result status and then block randomized to one of two study arms. Participants with CLIA lab reports indicating VUS or other complex results (e.g., possibly mosaic, suspicion for clonal hematopoiesis of indeterminate potential (CHIP), reduced penetrance variants) are excluded from randomization and redirected to an option to learn their results from a genetic counselor via telephone. All discordant results (original research result versus CLIA lab result) are evaluated by the genetics team to determine eligibility for randomization.

2.4. Protocol for Returning Genetic Research Results

All participants enrolled in the trial receive cancer genetics education prior to the option to learn their genetic research results. Modality of education and disclosure of genetic research results is based on study arm (see below). Pre-disclosure education includes content areas recommended by the National Society of Genetic Counselors [40] and used by others in *BRCA* trials [13, 41] and contains coverage of cancer types associated with

pathogenic variants in *BRCA* and other hereditary cancer genes, associated cancer risks, benefits/limitations of learning results, possible test results, implications of learning results for family members, and information related to genetic discrimination. Those who choose to learn their results following pre-disclosure education are provided with general management guidelines associated with the test result and additional resources. Additionally, participants receive a packet in the mail with a summary letter of their results, a gene details sheet (for any pathogenic/likely pathogenic results) and a copy of the CLIA lab report. Participants are also provided with an information packet to share with their health care provider, which includes a summary letter from the study team, a copy of the CLIA lab report, and National Comprehensive Cancer Network (NCCN) Guidelines® for any gene(s) with a pathogenic/likely pathogenic result.

2.4.1. Conventional (Control) arm—Women randomized to the conventional arm are contacted by study staff to schedule a call with a genetic counselor on the study team. Genetic counselors will provide the pre-disclosure education and then offer participants a choice to either learn their genetic research result or decline to learn. The genetic counselor will also track the length of session, questions/concerns voiced by participants, outcomes of the counseling, and counselor satisfaction with session. Reasons for choosing to decline results, if applicable, are noted by the genetic counselor. All telephone calls between study participants and the genetic counselor are audio recorded to assess fidelity to the counseling disclosure checklist and to provide additional data on participant questions, concerns, comprehension, and any misunderstandings. To ensure confidentiality, the genetic counselor will verify the participant's name, date of birth, and state they are currently located in prior to starting the audio recording. The audio file produced from any phone call will be labeled only with the patient's unique study ID. The audio files will be stored on a secure drive that is only accessible by BWHS research staff that are IRB approved for the study.

2.4.2. Online self-guided (Intervention) arm—Women randomized to the online arm are directed to view pre-disclosure education information via a secure web portal. Participants are required to enter their unique study ID and their date of birth, to access the portal. Once they are logged in, participants can review background pre-disclosure education sections at their own pace, after which they are presented with a choice to proceed within the website to learn their genetic research results or to stop and decline learning results. (Participants can return to the portal for up to 12 months if they change their mind and later wish to learn their results.) If there are women randomized to the online arm who cannot or prefer not to access the web portal, they are mailed the same pre-disclosure education information in print format and prompted to contact the study team via email or phone to request their genetic results in print. All participants in the online self-guided arm also have the option to schedule a call with a genetic counselor to discuss their results and/or address any concerns or questions they may have prior to or after learning their results. Calls occurring prior to learning results online will focus on addressing questions related to pre-disclosure education content only. Genetic counselors are blind to the genetic research result during these calls to prevent the unintentional disclosure of any results to participants in the online arm. All telephone calls with the genetic counselor are audio

recorded. Individualized genetic counseling similar to a clinical encounter is not provided in this research setting.

2.6. Data Collection

In addition to the baseline survey completed as part of enrollment, study participants are asked to complete follow-up surveys at 6 weeks, 6 months, and 12 months following their decision to learn their genetic research results. The decision to learn genetic research results will be tracked by the genetic counselor (conventional arm) and via the web portal (online self-guided arm). Participants who decline to learn their results are asked additional survey items to assess reasons for declining to learn results. The selection of study measures and the timing of their administration was guided by our conceptual model (Figure 2, see Theoretical Framework below) and informed by prior studies examining the clinical utility of *BRCA* counseling and testing in a clinical context [11, 42, 43]. Table 1 lists the study constructs being measured and their measurement time points.

2.5. Theoretical Framework

This study is guided by a framework of self-regulation, which has been extensively applied to inform understanding of decision-making processes in the context of genetic testing [15, 44–46]. In particular, this theoretical framework outlines the importance of both cognitive and affective processes, which together influence decisions to engage in genetic testing (i.e., learn results) and responses to genetic risk information. Recent conceptualizations have outlined important self-regulation principles that are relevant within the context of how individuals understand and respond to genetic information: *cognitive representations* (perceived risk/benefits/control, fatalistic beliefs), *emotion regulation* (anxiety, distress), *defensive processes* (avoidance, reactance), *temporal orientation* (value of future events), and *self-regulatory capacities* (e.g., literacy/numeracy, access, social norms, ability to engage)[44]. Constructs related to these self-regulation principles are being assessed in efforts to examine how they independently might explain acceptance/uptake of genetic information, and downstream responses to learning (or not learning) genetic risk (i.e., clinical utility).

2.7. Data Analysis

This study has one primary aim and two secondary aims. Hypothesis tests will employ a two-sided alpha level of 0.05. Tests of non-inferiority for primary outcomes will employ one-sided 99% confidence limits (97.5% confidence for secondary outcomes) and will compare these to non-inferiority margins used in the literature specific to the measures of interest [8, 11, 12, 34, 47]. For the primary aim comparing the efficacy of the two communication modalities for returning hereditary cancer predisposition genetic research results, we will examine the non-inferiority of the online self-guided modality as compared to the conventional modality using standard methods for tests of non-inferiority. As employed in the literature in similar studies of non-inferiority, particularly in the genetics context, each measure will require the establishment of its own non-inferiority margin (NIM) that is based on the consideration of a clinically meaningful difference between study arms in that outcome measure. These differences can then be computed in terms of a standardized effect size for means of a measure at a specific time point or a change

from baseline for that measure. The standardized effect size allows for interpretation that incorporates the inherent variability in each measure. In the case of an outcome on a nominal scale, we employ non-inferiority margins defined as clinically meaningful differences in proportions established in the literature. First, for those eligible and enrolled in the study, we expect a 75% test result uptake rate [42, 48, 49]. For this outcome, we will employ a 10% difference in proportions between study arms as the NIM consistent with prior published work [47]. The remaining outcomes will be assessed among those who proceed and learn their test results. For breast cancer genetics knowledge, we will assume a NIM of 0.2 in standardized effect size that is equivalent to a 1 point difference in means [8, 11, 12, 47]. For psychological distress (anxiety/depression), the NIM margin will be set at a standardized effect size of 0.33, consistent with a 0.53 point difference on the GAD, and an effect size of 0.36 for a 0.28 point difference on the PHQ-2 [50, 51]. For test-specific distress, we will employ a NIM of 0.43 in standard effect size, or a 1 point in the MICRA [8]. Finally, for uncertainty, the NIM will be 0.88 in standardized effect size [52]. We will apply one-sided hypothesis tests at the 0.01 level in declaring non-inferiority to reflect our examination of multiple endpoints (applying a Bonferroni-Holm correction [53]). We will apply intention-to-treat (ITT) as our primary analytic principle. In supplemental per protocol analyses, we will additionally examine outcomes separately for online- and print-based self-guided modality vs. conventional modality.

We will also conduct similar non-inferiority analyses of a set of secondary outcomes employing the same methods as for our primary outcomes. These secondary outcomes will include decisional outcomes (decision satisfaction/regret, satisfaction with communication modality) and behavioral outcomes (communication with family, communication with health care provider, screening, surgery). Using prior studies as a guide [8, 11, 12, 47], we will set conservative non-inferiority margins for these secondary outcomes of 0.5 of a standard deviation in differences in means or 10% in differences in proportions between study arms. We will apply alpha levels of 0.05 for analyses of these secondary outcomes.

To examine potential moderators of intervention impact, we will examine potential effect modification for result uptake, knowledge, psychological/test-specific distress, and uncertainty following test result in the context of linear models and apply one-sided hypothesis tests at the 0.025 level. We will also examine for potential confounders, although confounding will be assessed in terms of changes in the estimates of group-level differences in outcome and not through hypothesis tests. Changes of greater than 10% in these differences will be judged to indicate confounding by individual confounders of groups of confounding variables (joint confounders).

To explore predictors of result uptake in addition to intervention effects, we will examine psychosocial predictors guided by our conceptual model. To identify the best set of predictor variables for result uptake, we will implement LASSO-based logistic regression analyses using PROC HPGENSELECT in SAS. Odds ratios, 95% confidence intervals, and p-values will be computed from these models.

2.8. Sample Size and Power

We estimate an overall enrolled sample of 916 women, with an estimated 686 (~75%) who will learn their genetic research results, based on prior estimates of uptake from studies disclosing *BRCA* results via telephone-based genetic counseling to Black women [75%, 48, 49] and to women participating in breast cancer genome sequencing studies [78%, 42]. Thus, the estimated sample size for analyses of our non-inferiority endpoints that are contingent on uptake is 686 overall, 343 per study arm. For all the primary outcomes examined, statistical power ranges from 80%−99%.

For logistic regression analyses exploring predictors of result uptake, we can estimate an odds ratio as small as 1.29 for a one standard deviation difference in the predictor for a generic Gaussian predictor from the set of those specified above with 80% power at a two-sided alpha of 0.05 with squared correlation with the other covariates in the model as large as 0.4. The smallest detectable odds ratio for a dichotomous predictor with equal distribution between groups is 1.72.

3. Results

Bioethical principles of autonomy and respect for persons, justice, non-maleficence, and beneficence were applied in the initial design of the online intervention, study protocol, and study workflow to address several ethical considerations, as well as when legal considerations and challenges emerged in subsequent study planning and implementation (see Figure 3).

3.1. *Autonomy and Respect for Persons:* Respect a person's right to make choices/take action based on personal values and beliefs

In efforts to ensure autonomy and respect for persons, this study set out to prioritize the online provision of genetic information directly to participants, to review at their own pace. Study participants have the option not to learn research results after reviewing the background (pretest) information about cancer risk and genetics. In addition, the involvement of a genetic counselor is optional for participants (in the online self-guided arm) to initiate. Finally, participants are encouraged to share their results with their health care provider and a provider information packet is provided to participants to support provider and patient decision-making. However, any engagement with health care providers is at the discretion of the participant.

3.2. *Justice:* Equitable treatment and distribution of benefits

To ensure access to ones' own health information, this study focused on overcoming barriers to the return of personal health information obtained during research studies. When the genetic research study was initiated in the BWHS, informed consent for the original biospecimen collection indicated that the biosamples were for research purposes only and that no personal health results would be returned. For this trial of results return, a revised informed consent was necessary. A new research study and consent was created that would permit the return of hereditary cancer gene results that may have personal health implications. Efforts to ensure justice and equitable distribution of benefits also focused

on accessibility of study materials. All online materials were designed following principles for plain language (plainlanguage.gov). Usability testing of online materials focused on literacy-related challenges. In addition, a print version of the website was created as an option within the online arm, to accommodate self-guided access for participants who may have lower digital literacy and/or are unable to access the information online.

3.3. *Non-Maleficence:* Do no harm, obligation not to inflict harm intentionally

Following the principles of non-maleficence, several protocol modifications were made as the study began. First, although our team had proposed to conduct CLIA confirmation testing of all positive results following results return, this approach was determined as unacceptable by the legal team at our institution. It was determined that genetic research results required confirmation at a CLIA-certified lab *prior* to return to participants. Moreover, unlike prior studies that have also returned genetic research results [42], our team was required to confirm *both* positive (pathogenic) and negative (benign) research results. Additional grant funding was necessary in order to accommodate the new requirement.

Second, chain of custody of the original sample provided to a research study biorepository was of concern to the study Data Safety and Monitoring Board (DSMB), and as such, the protocol was revised to obtain a new sample for CLIA-certified lab testing rather than send DNA stored at the BWHS biorepository. Although this decision resolved the most pertinent chain of custody concerns, this change further increased expenses and may inadvertently reduce study enrollment as it requires additional steps and saliva sample collection from participants.

Finally, to reduce the risk of any harm from online disclosure of complex results that require more nuanced discussion, all CLIA-certified lab results of variant of uncertain significance (VUS) or other complex result (e.g., possibly mosaic) will be returned by a genetic counselor. Participants with these results will not be randomized within the trial; however, they will be surveyed over time to determine the clinical utility of this information.

3.4. *Beneficence:* Do good, provides benefits to others

To ensure beneficence and benefit to participants, we include 18 high- and moderate-penetrance cancer susceptibility genes for results return. Evidence of clinical utility based on actionable clinical management guidelines from the National Comprehensive Cancer Network (NCCN)® (https://www.nccn.org/) informed the selection of a final 18 genes for inclusion, expanding the study beyond a focus on breast cancer to include other cancers with a hereditary component. In addition, genetic counselor licensure was obtained by a study genetic counselor across all U.S. states that require genetic counseling licensure where BWHS participants reside (24) to allay any concerns that return of results from a CLIA-certified laboratory in a research setting across state lines could violate state licensure law(s). Finally, our study team is continuously tracking NCCN Guidelines® to provide current gene-specific materials and resources to both study participants and their providers over the duration of the trial period.

4. Discussion

This study will formally test an innovative method for returning genetic research results to a unique cohort of Black women and determine its impact on result uptake as well as the clinical utility of testing, the latter of which has not been well documented for Black individuals. Study results will provide evidence on the efficacy of using online self-guided approaches to return genetic research results in comparison to conventional methods and the clinical utility of providing genetic testing results among a large sample of Black women. It will also generate evidence on the most efficacious means to return research results in large, geographically dispersed, cohort studies, and enhance our understanding of the factors that explain why Black women choose or decline to learn their genetic research results.

A strength of this study is the projected large sample size for the trial, which allows for a more extensive study of the clinical utility of cancer genetic results for Black women, compared to much smaller sample sizes (e.g., n=215 or less) observed among Black women followed either prospectively or in clinical trials [43, 48]. This study will also provide insight into reasons for any differential uptake of testing across different counseling modalities, observed previously for non-white study participants [11, 54], by examining moderators of intervention impact and predictors of learning test results, guided by a strong theoretical framework.

This work builds upon limitations of prior research efforts including lack of non-white representation (and thus generalizability) in genomic research [8] and lack of design rigor in prior evaluations of online modalities (i.e., prospective, non-RCT)[21, 55], with few exceptions [8, 10, 56]. Additionally, the present study is testing different modalities for returning negative results, which are often returned using a different modality (e.g., print/mailed) compared to positive results, under the assumption there is less risk for harm [57]. Yet, prior work has also reported that return of results via a mailed letter, often done for efficiency reasons, has not been without challenges [58], further demonstrating the need to evaluate the impact of different modalities for returning negative results.

5.0. Conclusion

This study is uniquely situated to provide critical empirical evidence on the efficacy of alternate modalities for genetic results return and provide further insight into the factors influencing uptake of genetic information related to cancer risk among Black women. Study findings will inform ongoing efforts to establish scalable approaches for effective return of genetic research results and increase access to personal health information.

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In memoriam of Deborah J Bowen.

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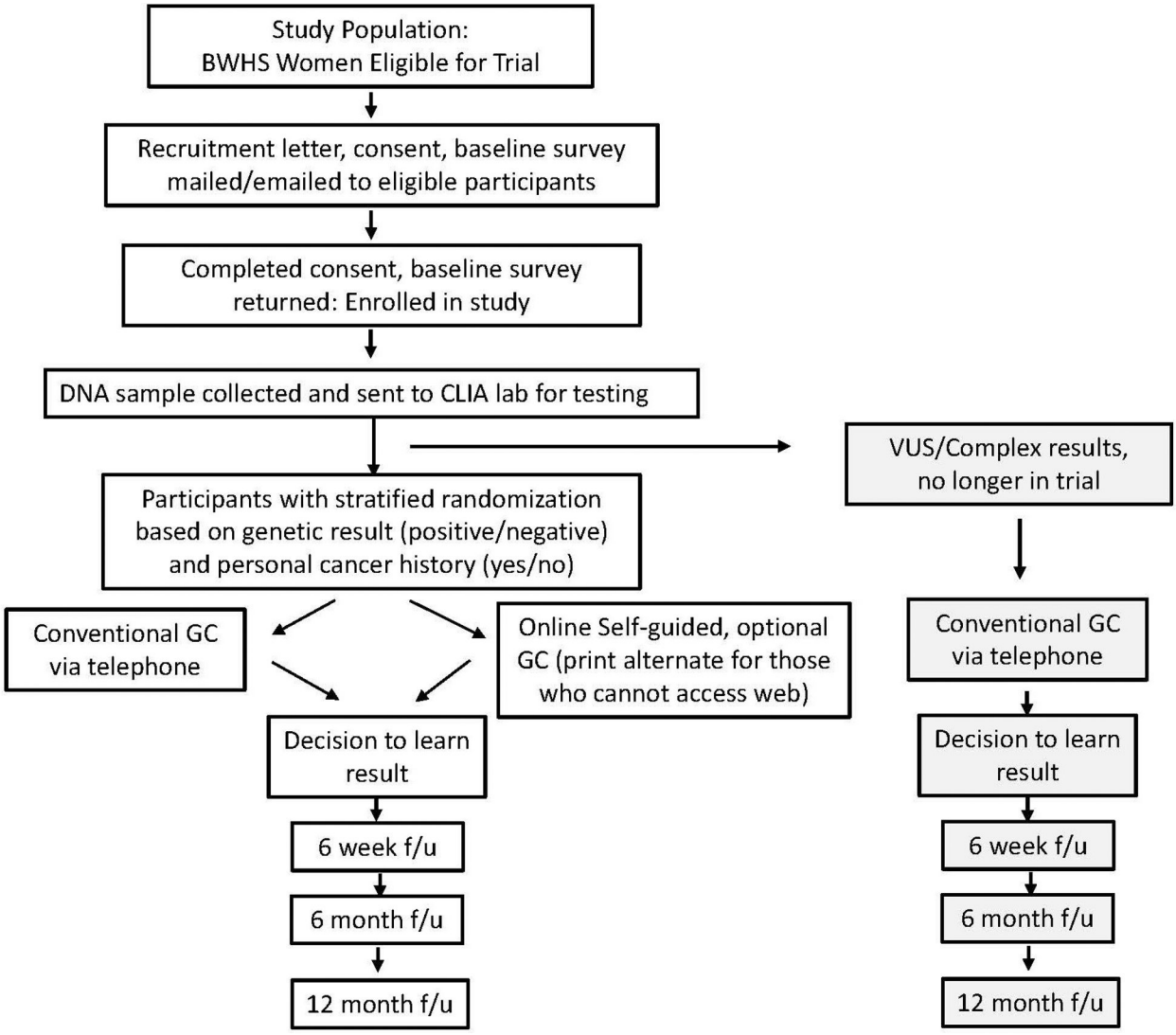

Figure 1:

CONSORT diagram showing the study workflow

GC – genetic counselor

f/u – follow up

VUS – variant of uncertain significance

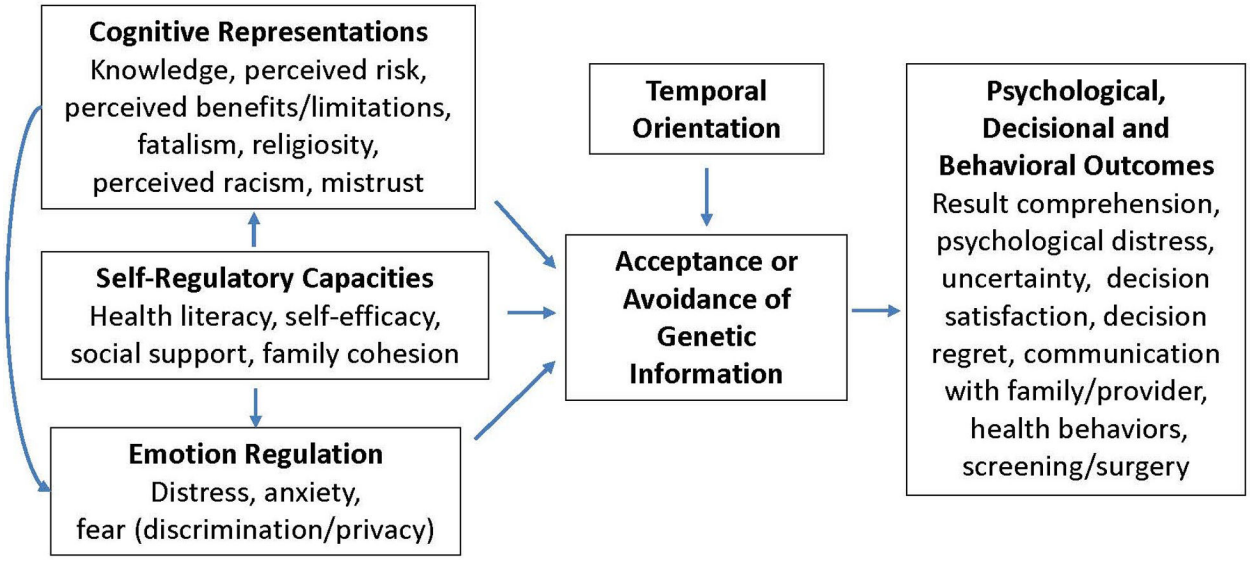

Figure 2.
Conceptual Model

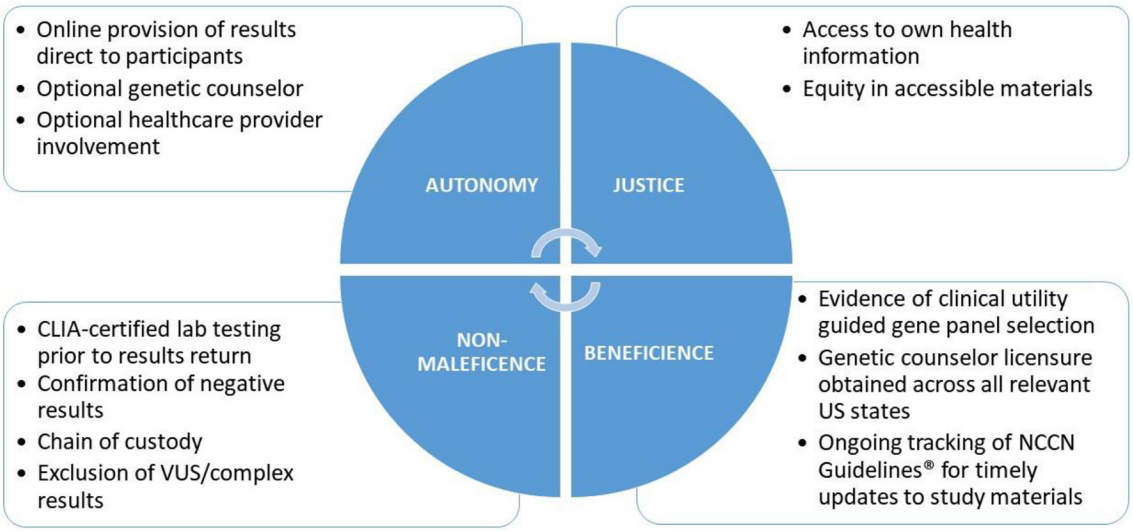

Figure 3.
Application of Bioethical Principles

Table 1:

Study Constructs and Measurement Time Points

Domain	Constructs	Time point*
Cognitive representations	Knowledge [47, 59–63]	T1, T2
	Perceived risk, benefits, limitations [46]	T1
	Medical mistrust [64]	T1
	Fear of discrimination [63]	T1
	Fatalism [65]	T1
	Religiosity	BWHS
Temporal orientation	Temporal orientation [66]	T1
Self-regulatory capacities	Health literacy [67]	T1
	Genetic self-efficacy [68, 69]	T1
	Family cohesion [70]	T1
	Financial toxicity/cost [71]	T1
Emotion regulation	Psychological distress (anxiety [72]/depression[73])	T1, T2
	Test-specific distress [52]	T2, T3, T4
Decisional/behavioral outcomes	Decision to learn result (test uptake)	BWHS
	Decision uncertainty [52]	T2, T3, T4
	Decision satisfaction/regret [74, 75]	T2, T3, T4
	Satisfaction with communication modality [8]	T2
	Reasons for declining to learn results	T2, T4
	Communication with family	T2, T3, T4
	Communication with health care provider	T2, T3, T4
	Reasons for not sharing results	T2, T4
	Health behaviors (screening/surgery)	T1, T3, T4

*T1 – baseline; T2 – 6 week follow up; T3 – 6 month follow up; T4 – 12 month follow up; BWHS (previously collected data from cohort or tracked in system)